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Could cheese be the missing piece in the French paradox puzzle?

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ABSTRACT

The low rates of cardiovascular mortality which have existed in France for decades despite high saturated fat consumption constitute an epidemiological phenomenon called the "French paradox". This phenomenon was originally attributed to consumption of red wine and its major constituent resveratrol. However, recent studies have revealed the limitations of this link outside France. These observations indicate that consumption of red wine alone cannot explain the paradox and perhaps some other constituents of the typical French diet could be responsible for reduced cardiovascular mortality. We hypothesize that cheese consumption, especially of molded varieties, may contribute to the occurrence of the "French paradox". This assumption is well supported by newly discovered facts revealing the positive effect of cheese ingestion on lipoprotein turnover and plasma lipid profile, haemorheological parameters and inflammatory status. Recent advances in cheese proteomics have allowed the identification and isolation of novel peptides capable of inhibiting the angiotensin-converting enzyme which controls systemic blood pressure. A complex time-dependent enzymatic transformation of the cheese core controlled by probiota, temperature and humidity during the ripening process has been shown to result in the formation of substances reducing major pro-inflammatory markers and cytokines (C-reactive protein, interleukin 6, tumor necrosis factor alpha). Molded cheeses, including Roquefort, may be even more favorable to cardiovascular health due to the presence of secondary metabolites produced by *Penicillium roqueforti* and other fungi. Among them are andrastins A–D and roquefortine, whose ability to inhibit cholesterol biosynthesis and bacterial growth may be a key mechanism in the prevention of cardiovascular disease.

Background

How can anyone govern a nation that has two hundred and forty-six different kinds of cheese?

Charles De Gaulle

Despite high consumption of saturated fat France still enjoys one of the lowest rates of cardiovascular mortality in the world, only falling behind Korea and Japan. According to the World Health Organization 2009 Mortality Database, the mortality from heart disease and stroke in France was 50 cases per 100,000 of population, whereas the rate in the USA approached 129/100,000. The geographic gradient in the occurrence of cardiovascular disease, translating into a 4-fold difference in the frequency of coronary vascular disease between Toulouse and Belfast, was first revealed by Dr. Samuel Black in 1819 [1] who noticed a striking statistical difference in the incidence of *Angina Pectoris* between Ireland and France. Indeed, despite its high consumption of saturated fat, France has a historically low rate of cardiovascular disease [2]. The introduction of the term "French paradox" by Serge Renaud in 1993 revitalized epidemiological studies which tried to explain the illogically low rates of cardiovascular mortality in France on the basis of red wine consumption by the French population [3]. However, besides red wine and its major constituent resveratrol, which seem to confer cardioprotective effects on wine drinkers [4], multiple other factors seem to be implemented in the French paradox. These include smaller portion size, lower number of eating occasions, regular gardening and exercise and higher intake of fruit and vegetables rich in flavonoids, phytosterols and dietary fiber [5–8]. Although a single causative factor explaining the occurrence of "French paradox" is unlikely ever to be found, the identification of contributory factors to reduced cardiovascular mortality in France would seem to be extremely important. In the present paper we hypothesize and argue that cheese consumption, especially of molded varieties, may contribute to the occurrence of the "French paradox".

French dietary pattern and Mediterranean diet

In general, French dietary pattern is characterized by meal preparation from basic/natural ingredients, structured mealtimes and less between-meal snacking [9]. Although there is significant

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diversity predetermined by regional, educational and socio-demographic factors [10], a typical French meal includes a significant amount of saturated fat originating from butter, cheese, whole milk and other dairy products, cured meats and pastries supplemented with some fruit and vegetables and moderate amounts of wine [11,12]. Dietary studies in France show that saturated fat may contribute up to 40% of total calorie intake [13]. On the other hand, the intake of fruit and vegetables is rather low especially in the Northern regions of France, comprising <300 g/day [14]. Although France belongs to the Mediterranean region, the true Mediterranean diet is found in very small geographical enclaves of Southern France. The Mediterranean diet is characterized by an abundance of fruit and vegetables, whole-grain foods, legumes, fish, olive oil and other unsaturated fats and moderate amounts of wine [12,15]. Notably, cheese is an integral part of both the typical French dietary regimen and the Mediterranean diet [16]. Cheese consumption in France (26.1 kg/capita) is one of the highest in the world, only falling behind Greece [17]. In general, besides unique taste, texture and versatility, cheese and its products have low glycemic index, high protein content and an abundance of vitamins (A, D, B6, B9) and minerals [18]. However, there was a persistent stigma attached to cheese due to its high saturated fat and cholesterol content [19]. Newly discovered facts about the nutritional pharmacology of ripened cheese products put a new light on the prospective use of cheese in the dietary management of human health and may help to establish a connection between reduced cardiovascular mortality and cheese consumption.

From milk to fermentated dairy and ripened cheese

At present the consumption of whole fat dairy products is severely disapproved of by the medical community since there is a strong correlation between consumption of unmodified dairy products and coronary heart disease which has been traced for decades [20]. In contrast, the ingestion of reduced fat dairy products has recently been proven to be beneficial in counteracting obesity as well as other manifestations of metabolic syndrome [21]. It has been claimed recently that the link between dairy consumption and cardiovascular disease needs to be re-evaluated [22]. Alpine cow milk and related dairy products rich in omega-3 fatty acids seem to promote a healthy lipid profile [23,24]. Fermented dairy products have obvious health benefits. The consumption of fermented milk products has been shown to be associated with a reduced risk of stroke [25], cardiovascular disease [26] and reportedly has a mild anti-hypertensive action [27].

For nearly a century, cheese was considered as a valuable dietary source of calcium for the human body [28]. However, beyond that, there is newly emerging information about the effects of cheese consumption on cardiovascular outcomes which can be difficult to explain. The first controversy relates to the well confirmed fact that despite extremely high lipid content [29], in particular of cholesterol, cheese intake is neutral or beneficial in terms of effect on plasma cholesterol, LDL and triglyceride levels [22,30,31]. Excessive cheese consumption has recently been reported [31] to reduce LDL cholesterol when compared with butter intake of equal fat content. Another enigmatic detail comes from research linking cheese consumption and inflammatory status. It has been shown that cheese, in particular commercial pecorino varieties which are rich in *cis*-9 and *trans*-11 conjugated linoleic acid, reduces plasma levels of tumor necrosis factor and interleukins 6 and 8 along with improvement of haemorheological parameters [32].

Although cheese proteomics still remains in its infancy, current research reveals that there are numerous biochemical events and transformations of milk-derived proteins and lipids which take place in the cheese core during ripening [33,34]. It is now recognized that proteolysis in the cheese core, initiated by probiotic bacteria and fungi [35,36], leads to accumulation of newly-formed peptides and macromolecules which could have a potential impact on the cardiovascular system [37]. As an example, some cheese-derived peptides have been shown to have an inhibitory activity on the angiotensin-converting enzyme, an enzyme controlling systemic blood pressure [38]. Cheese is a potential source of some other peptides which regulate thrombocyte functions, coagulation cascade and microcirculation [39]. Moreover, cheese consumption in a multi-dairy regime has recently been shown [40] to reduce the inflammatory markers of cardiovascular disease (C-reactive protein, interleukin 6, tumor necrosis factor).

It also appears now that the advantageous properties of cheese appear dynamically during the ripening process. Cheese which has been ripened for longer has been shown to be more effective in restoration of glucose tolerance, prevention of steatosis and adipose tissue oxidative stress than short-ripened specimens [41]. This data suggests that organic substances responsible for the health benefits of cheese emerge not merely due to mixing the ingredients required for cheese production, but rather as a result of a complex time-dependent enzymatic transformation of the cheese core controlled by probiota, temperature, humidity and possibly other factors.

Molded cheese, fungi and cardiovascular health

Roquefort, Camembert and Gorgonzola are only a few among many other varieties of popular molded cheese. In general, their production starts with the addition of rennet and a starter culture of *Penicillium roqueforti* or *Penicillium camemberti*, fungi which promote flavor formation in the full cream sheep's milk [42]. The biochemistry of the ripening of these cheeses is far more complex than that of bacterial-ripened varieties such as Cheddar or Gouda and is characterized by more intense proteolysis [43]. As a result, the core of ripened molded cheeses contains a unique variety of substances of mammalian, bacterial and fungal origin that are not present in other cheeses. In particular, Roquefort and other blue cheeses contain andrastins A–D which are potent inhibitors of farnesyltransferase, a major enzyme of cholesterol biosynthesis [42]. Andrastin A is also known to display strong anti-tumor activities, suggesting its anti-cancer potential [44]. Other substances, including roquefortine, have strong anti-bacterial properties and inhibit Gram-positive bacterial growth through cytochrome P-450 [45].

Conclusion

The link between wine consumption and reduced cardiovascular mortality is not straightforward. Despite the persistent nationwide decline in wine consumption [46], France continues to show remarkably low levels of cardiovascular mortality. On the other hand, growing demand for red wine in the countries of Eastern Europe (*Wine Annual Report and Statistics, U-27, 2011*) does not affect the alarmingly high rates of cardiovascular disease in the region [47]. Therefore, "French paradox" seems to be a multifactorial phenomenon and not solely due to red wine intake.

Cheese and cheese-based products are essential and indispensable ingredients of the typical French and Mediterranean diets. Both of these diets are characterized by low cardiovascular mortality. Regular cheese consumption unifies all regional dietary cultures in France. Moreover, as we discussed above, there is a growing body of epidemiological, clinical and experimental evidence suggesting that regular cheese intake may reduce the risk of cardiovascular outcomes. As we mentioned above, newly discovered cheese-derived peptides inhibiting the inflammatory cascade and

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angiotensin-converting enzyme may provide a pharmacological basis for this phenomenon. Therefore it is plausible to conclude that cheese consumption might be an important factor in conferring resistance to cardiovascular disease in the French population. This statement is well supported by the fact that other European countries with similarly high cheese consumption (Switzerland, Greece) have a lower incidence of cardiovascular disease and mortality [18,47,48]. Moreover, there is a distinct north–south gradient across Europe in the incidence of cardiovascular mortality which is traditionally explained by lifestyle variations [48]. Among these are dietary factors, and cheese consumption in particular may play a crucial role. Paradoxically, southern regions of France, Italy and Greece are geographical enclaves of Europe with historically established cheese-making activity, especially of molded blue cheeses. Scrupulous epidemiological analysis, experimental and clinical studies are required to verify any such link between blue cheese consumption and cardiovascular health. However, in our opinion, there is great and as yet poorly acknowledged promise in the dietary use of blue-veined cheeses. It is obvious that besides vasoactive peptides attributable to bacterial-induced modification of the cheese core, Roquefort and other blue-veined cheeses contain some important secondary metabolites produced by *P. roqueforti* and other fungi. As we stated above, recent advances in molecular science have revealed a wide variety of secondary metabolites of *P. roqueforti* – andrastins A–D as well as roquefortine, whose ability to inhibit cholesterol biosynthesis and bacterial growth might be a key mechanism in favoring their therapeutic potential for cardiovascular disease [49]. If the use of blue-veined cheeses in dietary management of cardiovascular patients does indeed hold the promise of measurable health benefits they need to be demonstrated in carefully designed clinical trials and experimental studies.

Conflict of interest statement

None declared.

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